Kinetically-Derived Maximum Doses

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Outline

- Incorporating Kinetic Data/Model in Risk Assessment
- Kinetically-Derived Maximum Dose (KMD)
  - Definition
  - Implication in Risk Assessment
- Case Study
- KMD-related Efforts

Kinetics in Risk Assessment: Dose Makes the Poison

- Risk assessment is the characterization of the potential adverse effects of human **exposures** to environmental **hazards** (NRC, 1983)
- Kinetics determines the movement of a chemical into, through, and out of the body; the time course of a chemical's absorption, distribution, metabolism, and excretion
- The internal target tissue dose determines the initiation and degree of toxicological responses
- Kinetics connects exposures to hazards

Value of Kinetic Data/Models

- Support smarter testing strategies
  - Reduce & Replace: eliminate duplicative testing or unnecessary studies
  - Refine: lessen animal suffering by not testing at doses that cause overt toxicity
- Quantify and reduce uncertainty in risk assessment
- Evaluate consistency with mode of action hypothesis
- Extrapolate points of departure across species, routes, life-stages, etc.

Examples of risk assessment applications in OPP

- Using physiologically based pharmacokinetic (PBPK) models to replace the use of default uncertainty factors for inter-species extrapolation, route-to-route extrapolation, and age-specific extrapolation
- Using PBPK models to estimate scenario-specific points of departure
- Using *in vitro* and *in vivo* dermal absorption measurement to adjust route-specific points of departure
- Using *in vitro* metabolism data to understand dose-response difference across species or life-stages
- Using kinetic data to interpret dose-response data or select doses in animal toxicity studies – kinetically-derived maximum dose (KMD) approach

KMD Definition

- KMD is the highest dose at, or slightly above, the point of departure from linear kinetics
- Non-linear kinetics can arise from various factors, such as saturation of absorption, metabolism, protein binding, excretion, resulting in chemical concentrations in the body to be disproportionally high or low relative to the change in external dose

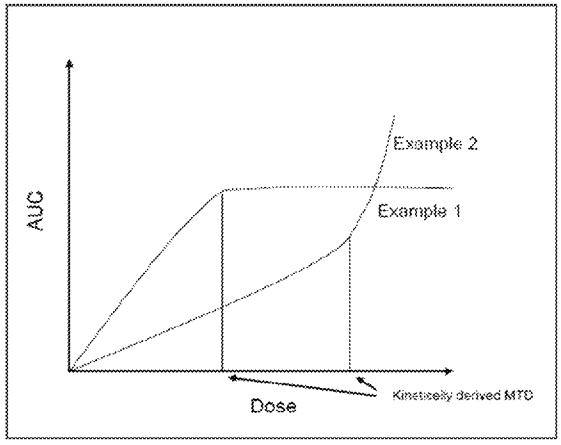

Figure adapted from 2008 REACH Guidance, Figure R.7.12-2

KMD Implications

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- When internal dose becomes disproportionally low relative to the change in external dose, "there is little point in increasing administered dosage if it does not result in increased plasma or tissue concentration" (ICH S5)

- When internal dose becomes disproportionally high relative to the change in external dose, "exposures in rodents, greatly in excess of the intended human exposure, might not be relevant to human risk; because they so greatly alter the physiology of the test species" (ICH S1A, S1B, S1C)

Case Study – Weight of Evidence Approach

- Study purpose: Understand if lung tumors observed in male mice at high dose (60 ppm) of telone are due to saturation of metabolic clearance
- Multiple lines of evidence suggest that systemic exposures in mice become non-linear at 30 ppm or above
  - Both a hockey-stick model and a power model conclude that area under the curve (AUC) of blood concentrations become non-proportional to external dose between 30-40 ppm
  - The cis- and trans-isomers of telone changes from 0.13 to 0.2 between the external concentrations of 40-60 ppm
  - The glutathione(GSH)-dependent metabolism of telone results in significant depletion of GSH at external dose 30 ppm and above

An International Effort – Developing Best Practices

- Under the MOU between EPA and Health and Environmental Sciences Institute (HESI), a KMD project is initiated in 2020 by the HESI PBPK Committee
  - Develop best practices and guidance on the KMD analysis
  - Discuss if and how KMD can be applied in the context of risk assessment
  - Identify situations where the use of KMD might be limited or prohibited
- A 3-day virtual workshop, co-sponsored by NICETAM, USEPA, and HESI, will be held on October 6-8, 2020
  - Address commonly raised technical and scientific issues related to KMD
  - Discuss best practices and lessons learned
  - Discuss the possible applications and limitations of KMD

Summary

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- A figure to summarize all five projects?